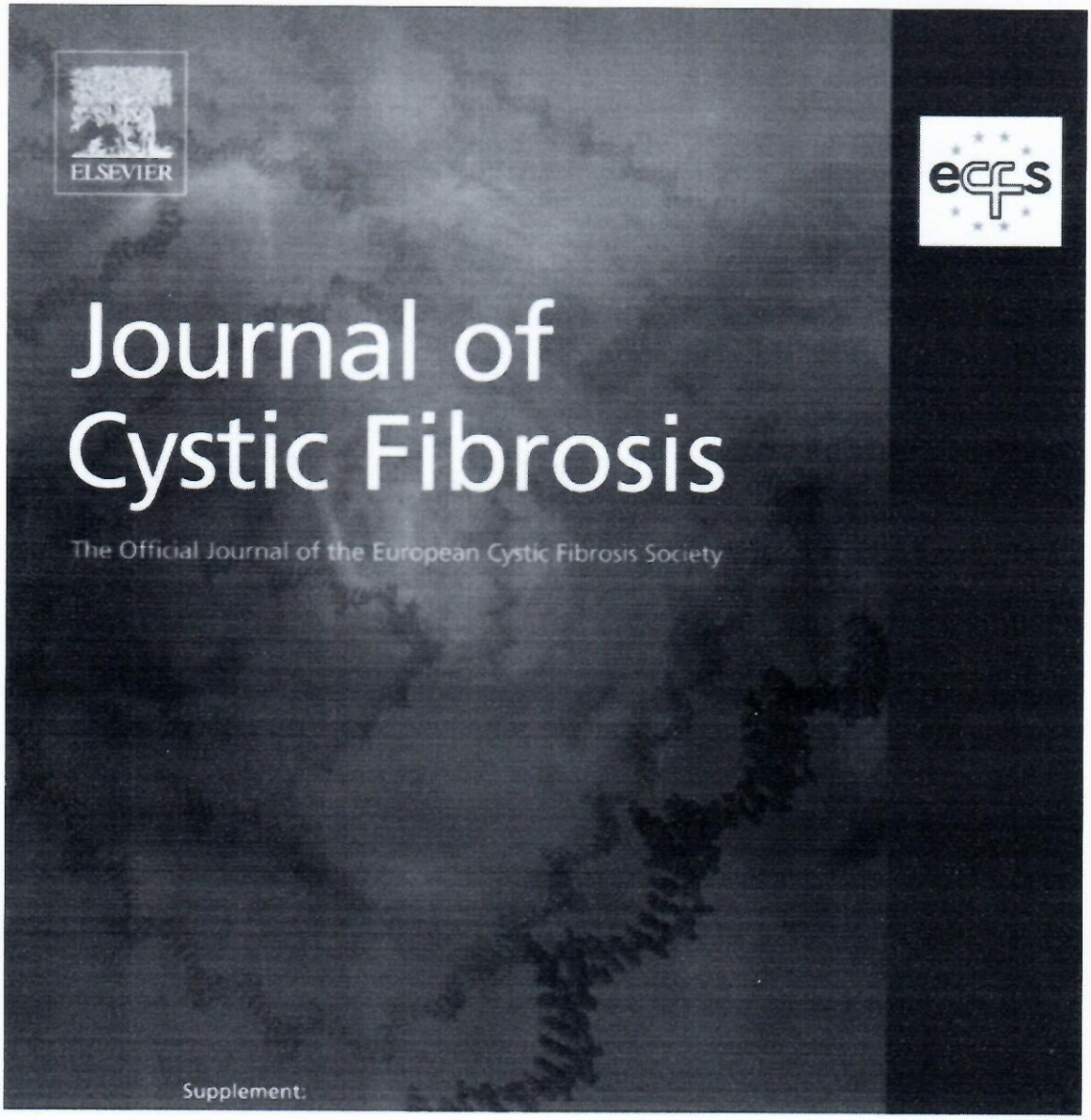

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analysed. Screen positive newborns (IRT>P99 and 1 or 2 mutations) were referred to a CF centre for measurement of SCI by quantitative pilocarpine iontophoresis. For IRT > P99.9 with negative mutation screening, a failsafe is provided with repeat IRT at day 21. CF centres provided diagnostic feedback to the screening labs.

Results: In 2019–2020, 125,732 newborns were screened (coverage 99.9%). 68 (0.056%) had raised IRT plus at least 1 mutation. CF was confirmed in 22/68 (6 with MI) plus in one newborn with MI but normal IRT, and in one newborn from the failsafe (no recall at day 21 was received), resulting in total of 24. 43/68 were carriers (normal SCI) and 3/68 were CF SPID (intermediate SCI). CF centres reported no missed cases. From 97 newborns with >P99.9, three had persisting elevated IRT on day 21 but all had negative SCI. Based on these results, sensitivity was 100% (1 MI with negative IRT excluded per protocol), PPV 0.32 (0.36 when calculated with CFSPID), and CF/CF SPID ratio was 7.6.

Median age at initial visit in the CF centre/diagnosis was 20 days, respectively 23 days.

Discussion: Performance of the program is in agreement with ECFS standards. The initial IRT cut-off had to be adapted (P99 on stored samples did not match true P99) explaining the high number of false positives in the first 2 months. We evaluate if we can increase the IRT cut-off to further improve the PPV.

It is a matter of debate if CFSPID should be incorporated in the calculation of the PPV or not.

P012

Two-year neonatal screening for cystic fibrosis in Republic of North Macedonia

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Objectives: Newborn screening (NBS) for cystic fibrosis (CF) was introduced as a national program on all newborn population in R.N. Macedonia from 2019, after a pilot study in 2018.

Methods: Two steps IRT-IRT algorithm is performed, and then a sweat test (Macroduct sweat collection system followed by Chloridometer chloride analysis) for confirmation/exclusion of the CF diagnosis when IRT values were both over the cutoff (70 ng/ml and 45 ng/ml, respectively). In cases of positive or borderline sweat tests, mutation analysis of *CFTR* gene is performed: snapshot reaction for 11 most common regional *CFTR* mutations or extended gene analysis: multiplex ligation-dependent probe amplification (MLPA), for detection of deletions/duplications, Sanger DNA sequencing or next generation sequencing.

Results: During 2019, 15,033 newborns were screened for CF. The diagnosis of CF was confirmed in 8 cases. One case with meconium ileus was missed on screening (false negative). During 2020, 18.757 newborns were screened for CF. The diagnosis of CF was confirmed in 4 cases. If we take into account the results of NBS-CF pilot study on 9,332 newborns (2018), when 5 cases of CF were diagnosed, it applies that the incidence of the disease is variable. In all newly discovered CF cases by screening, the diagnosis was confirmed by determining of CFTR mutations. The most common CFTR mutation F508del was found with an overall incidence of 70.6%. Other more frequent mutations were G542X (11.8%) and N1303K (5.9%). Four mutations were found in one CFTR allele each (G1349D, G126D, 457TAT>G and CFTRdupexon22), with the last one being newly discovered with unknown consequences.

Conclusions: Our first experiences with NBS gives us promising results and objective hope for keeping patients in good health condition.

P013

Evaluation of improvements of the cystic fibrosis newborn screening protocol in the Netherlands

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In 2011 a four-step protocol was implemented for screening for cystic fibrosis (CF) in the Netherlands. Immunoreactive trypsinogen (IRT) was measured in all dried blood spot cards. Pancreatitis-associated protein (PAP) was conducted for samples with IRT ≥ 60 µg/l. INNO-liPA line probe assay (35 mutations) was performed if IRT ≥ 60 µg/l&PAP ≥ 3.0 µg/l or IRT ≥ 100 µg/l&PAP ≥ 1.6 µg/l. When DNA analysis revealed one CF-causing mutation, or no mutations in combination with IRT ≥ 100 µg/l, an extended gene analysis (EGA) was performed. Children with one or two CF-causing mutations or two mutations with unclear clinical relevance were referred to a CF centre. An evaluation of this protocol (Dankert-Roelse, J Cyst Fibros. 2019; 18:54–63) reported a low sensitivity of 90%, with 16 missed patients on 819,879 screens (0.0019%) between 1 May 2011 and 31 December 2015. New cut-off values were recommended and implemented from July 2016. The lower cut-off value for PAP was changed to 1.2 µg/l and a new safety net was introduced. The third tier now is performed in combinations of IRT ≥ 60 µg/l&PAP ≥ 3.0 µg/l, IRT ≥ 100 µg/l&PAP ≥ 1.2 µg/l or in case of an IRT ≥ 124 µg/l independent of the PAP concentration.

Between 1 July 2016 and 31 December 2019 599,137 screens were performed, of which 128 (0.02%) children were referred because of suspected CF. Six children, all diagnosed with CF, were referred based on the new safety net where high IRT results in DNA analyses, regardless of the PAP. Five children, diagnosed as carriers, were referred based on the lower cut-off value for PAP (≥1.2 µg/l).

Despite the changes, to our knowledge five children (0.0008%) were missed during screening between July 2016 and the end of 2019. Two of these children had low IRT. The others had IRT&PAP combinations that were not high enough to start the third tier. At least one of these children had meconium ileus (MI).

The changes to the screening program resulted in a sensitivity of 95%, with a positive predictive value of 77%.

P014

Are lower respiratory tract symptoms different in children with high immunoreactive trypsinogen levels?

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Objectives: Neonatal screening for cystic fibrosis (CF) is composed of blood immunoreactive trypsinogen (IRT) measurements in Turkey. Increase in IRT levels is an indicator of cystic fibrosis transmembrane regulator protein (CFTR) dysfunction. Thus, respiratory tract diseases may be more frequent and severe due to possible CFTR dysfunction in newborns with high IRT values but not cystic fibrosis. Therefore, the aim of this study was to evaluate the respiratory problems encountered in children detected to have two high levels of IRT levels at the neonatal screening differ from normal population.

Methods: We enrolled children referred to our centre for CF evaluation with sweat test after detection of high IRT levels at the neonatal screening program between 2015 and 2020. We recorded current age, sex, IRT levels and sweat chloride levels from the files. Moreover, we contacted the families by phone and asked if these children ever had lower respiratory tract symptoms such as wheezing or were diagnosed with pneumonia or

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We thank you for your participation,

Isabelle Fajac
ECFS President